

The Genetic Basis of Idiopathic Pulmonary Arterial Hypertension

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Idiopathic Pulmonary Arterial Hypertension (IPAH) is a rare autosomal disease that affects 1 in 500,000 people. IPAH can be classified as sporadic or familial. The disease is characterized by occlusion of the pulmonary arteries due to vascular proliferation. The vascular proliferation combined with a down regulation of smooth muscle cell apoptosis leads to a vascular remodeling that restricts blood flow through the lungs and results in chronically high pulmonary arterial pressures. Chronic pulmonary arterial hypertension places a strain on the right ventricle of the heart, leading to right ventricular hypertrophy and eventually failure. Recent studies indicate that mutations in the bone morphogenic protein receptor II (*BMPR2*) gene may be linked to the development of IPAH. *BMPR2*, a member of the transforming growth factor beta family, plays a key role in inhibiting cell growth and has been indirectly linked to cellular apoptosis.

The aim of our study was to identify novel single nucleotide polymorphisms (SNPs) in the *BMPR2* gene of IPAH patients, and to investigate whether SNPs in the *BMPR2* gene can be correlated to the occurrence of SNPs in other candidate genes (*KCNA5*, *TRPC6*, *ANGPT1*, and *SLC6A4*) in the development of IPAH. Genomic DNA samples were collected from a total of 45 IPAH and non-IPAH patients. Exons 1, 8, and 13 of the *BMPR2* genes of these patients were re-sequenced using PCR amplification and gel purification. Exons 1, 8, and 12 were particularly chosen because of their locations in the extra cellular, kinase, and cytoplasmic tail portions of the *BMPR2* gene, respectively the sequences were then examined for novel and previously identified SNPs. Of the 45 patients, one patient had a SNP located in the promoter region of the *BMPR2* gene which alters the binding site of transcription factors *MZF1*, *GATA1*, and *ADR1*. Altering these transcription binding sites may lead to the down-regulation of *BMPR2*. A previously identified synonymous SNP was located in Exon 12 in 2/45 patients. The remaining exons of the *BMPR2* gene still remain to be re-sequenced in these 45 patients, at which point the SNPs found (in addition to the SNPs reported above) will be correlated to SNPs in the other candidate genes in the development of IPAH. Further research will reveal whether any of these SNPs cause down-regulation of *BMPR2*, in which case we may be able to draw a direct link between the SNPs and the medial hypertrophy that leads to the development of IPAH.